Remarks

Supplemental Information Disclosure Statement

Applicants wish to bring to the attention of the examiner the following art cited by the examiner during the prosecution of U.S.S.N. 09/858,016:

U.S. Patent No. 5,702,723 to Griffin ("Griffin")

U.S. Patent No. 4,661,492 to Lewis *et al.* ("Lewis")

U.S. Patent No. 4,814,181 to Jordan *et al.* ("Jordan")

GB 800,973 to Sterling Drug, Inc.

The examiner in the related case has also requested a terminal disclaimer in view of the claims in this application.

Amendments to the Claims

Independent claims 1, 20 and 21 have been amended to insert a definition of the first oral component as having a molecular weight of less than 350 daltons, in a dosage of no more than about 50 mg, which is released rapidly.

Support for these limitations is found page 9, line 11 (dosage to 50 mg for intraoral dosing); page 10, line 5, (up to 350 daltons); page 9, line 22 (released rapidly).

Claim 14 has been amended to correct a typographical error.

Claim 16 has been amended into independent form, specific to three drugs, buprenorphine, fentanyl, or ergotamine.

Claim 2 is cancelled as failing to further limit claim 1. The dependency of claim 5 has been corrected. Claim 6 has been amended to correct the claim language as definite.

Entry of these amendments is earnestly solicited to place the claims either in condition for allowance or in better position for appeal.

Rejection Under 35 U.S.C. § 103

Claims 1-23 were rejected as obvious under 35 U.S.C. 103(a) over U.S. Patent No. 6,294,199 to Conley et al. ("Conley"). Applicants respectfully traverse the rejections.

It is believed it would be helpful to respond first to some of the examiner's comments, in particular regarding Conley that "... language does suggest the active agent in the immediate release layer disintegrates rapidly in the mouth, and therefore, provide intraoral absorption". A clear distinction needs to be made between two different scenarios: (a) drug is released within the oral cavity and *absorbed within the oral cavity (intraoral absorption)* and (b) drug is released within the oral cavity, then swallowed with saliva, and finally *absorbed in the GI tract.* To be suitable for intraoral absorption drug needs to meet the following criteria:

molecular weight smaller than 350 daltons

small dose (up to 30-50 mg)

high and rapid aqueous solubility.

These are the features discussed in the applications as critical to intraoral absorption *and previously argued as the features distinguishing the limitations defined by the claims as previously examined*; these limitations have now been explicitly inserted into the claims.

Amoxicillin is NOT suitable for intraoral administration since its molecular weight is above 350 and, more importantly, is only slightly soluble in water (solubility is

4.0 mg/ml (see Merck Index, 12th Edition, MN 617)) and therefore not rapidly released. Additionally, due to amoxicillin pKa values (amine 7.49, COOH 2.68, and phenol OH 9.63), drug is absorbed most efficiently only after passing through the stomach and entering the small intestine having a pH 3-6 (above normal stomach pH), where the net charge of amoxicillin is zero (Nichols, W.K., Anti-Infectives. In: Gennaro, A.R. et al.: The Science and Practice of Pharmacy. 20th Edition. Baltimore: Lippincott, Williams, and Wilkens, 2000: 1520). No amoxicillin will be absorbed in the mouth since the oral cavity has a normal pH of 6.5. Moreover, the evidence that amoxicillin is not absorbed in the oral cavity is presented by Conley in Figure 3. T_{max} of the various tested formulations of amoxicillin produced *in vivo* is between 1 and 2 hours, which is substantially higher than that of sublingually absorbed drugs (T_{max} in the minute range). The therapeutic dose of amoxicillin is between 1900 and 2600 mg as described by Conley et al. (col. 8, lines 44-57; Claim 1 of US Patent No. 6,294,199), not less than 50 mg.

Conley does not make it obvious to a person ordinary skilled in the art to combine in one dosage form drugs for *intraoral* and *oral administration* since Conley does not describe an immediate release layer that dissolves intraorally and amoxicillin is not a drug suitable for intraoral administration.

Further, the active ingredients of applicants' claimed composition and method are systemically acting agents that are absorbed into the bloodstream at two different sites of the human body: the first ingredient within the oral cavity and the second ingredient within the GI tract. Conley specifically states that "part of the challenge in providing formulations of amoxicillin ... is the relatively narrow window for **absorption of the drug in the small intestine**" (column 4, lines 33-37). Therefore, even if the composition

described by Conley releases some amoxicillin in the mouth due to disintegration of the IR layer (column 11, lines 45-60) or when tablet is chewed (column 17, lines 25-65), the drug's absorption will occur in the small intestines, and it will not achieve meet the claimed limitations.

With respect to the method of claim 21, amoxicillin provides its therapeutic effect to the patient regardless of the way tablet is administered, i.e. swallowed, kept in the mouth and then swallowed, chewed and then swallowed, etc. In contrast, claim 21 requires the tablet be kept in the mouth until the intraoral portion is dissolved. This is essential or the dose of the drug intended for intraoral administration will not enter systemic circulation via transmucosal absorption in the oral cavity. Since most of the drugs intended for intraoral administration are unstable in the environment of the human GI tract (e.g. nitroglycerin), the patient will not benefit from the therapeutic effect of the intraoral drug if the tablet is swallowed without allowing the triturate to dissolve within the oral cavity.

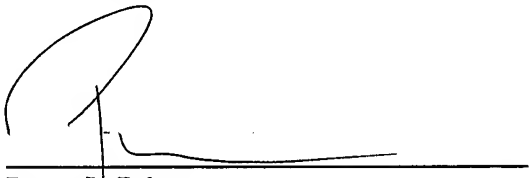
In summary, Conley does not make obvious either the claimed formulation or method of manufacture or use, since Conley does not disclose the claimed features, nor the problems that would lead one to modify and combine the claimed features as applicants have done.

Moreover, Conley does not recognize the problems with the conventional delivery formulations that applicants address and solve. The claimed dosage form for intraoral/oral administration has advantages compared to conventional triturate tablets, which are fragil due to inherent softness. In the claimed intraoral/oral dosage form, the triturate portion in the center of the tablet is "protected" from mechanical damage by a

surrounding layer of compressed tablet. The manufacturing process defined by claim 20 that is used to produce the intraoral/oral dosage form is different from that normally used to produce compressed conventional or bi-layer tablets. Conley completely fails to address these issues. Accordingly, Conley fails to make obvious the claimed method of manufacture.

Allowance of all claims 1-23 are earnestly solicited.

Respectfully submitted,



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